REMARKS/ARGUMENTS

Status of the Claims

Claims 53, 58-72, 74, and 77-97 were previously pending in the application. Claim 96 is amended. Claims 65, 66, 68, 69, 72, 73, 89, 90, 92 and 96 are canceled herein without prejudice. Claims 98, 99, and 100 are newly presented. After entry of these amendments. claims 53, 58-64, 67, 70, 71, 74, and 77- 88, 91, 93 to 100 will be pending.

Claims 53, 58-72, 74, and 77-97 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly lacking enablement.

The Applicants respond to this rejection below.

Support for the amendments to the claims

New claim 98 finds support at page 61, lines 8 to 9 of the original specification and at page 71, lines 10 and 11 of the substitute specification.

New claim 99 sets forth subject matter finding support in previous claim 53.

New claim 100 depends from claim 78 and sets forth the immune response is a humoral immune response. This subject matter finds support in the original specification at page 61, line 26.

Accordingly, the Applicants believe the amendments to the claims add no new matter and respectfully request their entry.

Response to the rejection for alleged lack of enablement

A. Standard of review

As noted earlier, whether undue experimentation is required to practice an invention is typically determined by the *Forman* factors. These factors weigh (i) The relative skill of those in the art; (ii) The nature of the invention; (iii) The breadth of the claims; (iv) The amount of guidance presented; (v) The presence of working examples; (vi) The state of the art; (vii) The predictability of the art; and (viii) The quantity of experimentation necessary. *Ex parte Forman*, 230 U.S.P.Q. 546 (PTO Bd. Pat. App. & Inter. 1986), *In re Wands*, 858 F.2d 731,

8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). The Applicant first address the particular points raised by the Action and next address each of the Wands factors, with respect to the amended claims.

Most of the concerns raised in the action relate to the induction of a cellular immune response. One concern raised by the Action is whether the length of the various peptide fragments set forth in the claims were too long to be active in inducing a cellular immune response. In fact, professionally antigen presenting cells such as dendritic cells digest proteins into smaller peptides. In the lymph node, the DC will display these antigenic peptides on its surface by coupling them to MHC Class II molecules. This MHC:antigen complex is then recognized by T cells passing through the lymph node. Exogenous antigens are usually displayed on MHC Class II molecules, which interact with CD4+ helper T cells. CD4+ lymphocytes, or TH, are immune response mediators, and play an important role in establishing and maximizing the capabilities of the adaptive immune response. Thus, the length of a fragment is *no* bar to its suitability in generating such responses. A large fragment can be processed to provide a number of different subfragments to be presented on the surface of an Antigen Presenting Cell (see Exhibit A, pages 115 to 119 of Roitt et al., *Immunology*, 5th Edition, Mosby press, Philadelphia). Some such fragments will be of a length of sequence suitable for binding to an HLA allele. This comports with the results of Kiessling et al., already of record, who found the presence of $CD8^+$ reactive cells which recognized two of their peptide fragments in the serum of cancer patients *who had not been administered the PSCA peptide fragments.*

A second concern raised in the action is the absence of clinical trials indicating any efficacy of a PSCA peptide vaccine. Thomas-Kaskel et al. have now reported the results of a clinical trial using $PSCA_{14-22}$ and PSA peptide-loaded dendritic cells to vaccinate advanced prostate cancer patients (see. Thomas-Kaskel et al., Intl. J. Cancer 119:2428-2434 (2006), enclosed with IDS). The study concludes:

> The experience from this trial argues that DC-based vaccination against PSCA in the dose range given seems worthwhile for further clinical testing as a vaccination antigen. However, immunosuppression is likely to prevent higher rates of immune responders unless active immunotherapy is being employed earlier in the course of the disease, for example in the

> setting of a ''PSA relapse'' after radical prostatectomy. The correlation of immune responses with superior overall survival, further supported by documented regression of lymph node metastasis or impressive subjective pain relief, suggests that tumor-specific cellular immunity may indeed provide clinical benefit in CaP, although the optimal time point and vaccination schedule need further clarification.

These results demonstrate, contrary to the Action, that the *in vitro* observations as to the PSCA peptides *are predictable* in translating to the clinic.

Moreover, the very existence of such clinical trials strongly evidences that persons of ordinary skill in the art felt the art was reasonably predictable and ought to be so viewed by the Examiner. Indeed, the MPEP §2107.03 at 2100-35 right column provides:

> ... In order to determine a protocol for phase I testing, the first phase of clinical investigation, some credible rationale of how the drug might be effective or could be effective would be necessary. Thus, as a general rule, if an applicant has initiated human clinical trials for a therapeutic product or process, Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility.

[underlining in the original].

Thirdly, the Examiner cites Kiessling et al. as finding that only 2 of 8 tested peptide fragments bound to the HLA-A-201. Nothing in Kiessling indicates that it took undue experimentation to identify such peptide fragments. They used standard models to identify 8 candidates and found 2 fragments to be active (i.e., $PSCA_{14-22}$ and $PSCA_{105-113}$). This hardly seems to involve and undue amount of experimentation. The steps performed are routine and the amount of experimentation required to identify 2 useful agents, simply *minimal* for this field of art. The standard for enablement is not whether *any* experimentation is required but whether the amount of experimentation is undue.[1]

[1] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

Without doubt, the pharmaceutical arts are one in which it is routine to screen a large number of agents in order to find useful ones. The expenditures of substantial sums to practice an invention is no bar to enablement. Indeed, in the context of dose response, the Federal Circuit held in 1988 that if a specification teaches one embodiment and sets forth a method for determining dose/response, the experimentation required to determine a dose/response curve is not undue, even if the studies proved to cost approximately $50,000 and took 6-12 months to accomplish. *United States v. Telectronics*, 8 USPQ2d 1217 (Fed. Cir. 1988), *cert. denied*, 490 U.S. 1046 (1988).

Previously, the Applicants cited Matsueda et al. as disclosing that one (i.e., $PSCA_{76-84}$) of three tested peptides was active. Applicants now enclose with their IDS another Matsueda et al. reference which reports on the finding that two out of an additional 11 PSCA peptides (i.e., $PSCA_{7-15}$ and $PSCA_{21-30}$) were active (see, Matasueda et al., *Cancer Immunol. Immunother*. 53:479-489 (2004)). Having found them, Matsueda et al. again state that their peptides should be considered for use in clinical trials in immunotherapy. Clearly, persons of ordinary skill in the art are able to repeatedly identify suitable peptide fragments without much experimentation at all and these persons view the obtained peptides as being credible candidates for immunontherapy. The last sentence of Kiessling et al. is in accord on this last point:

> Our results emphasize the suitability of PSCA target molecule for the immunotherapy of prostate cancer.

As a fourth concern, the Action contends that the Applicants have not addressed the 'general' concerns raised by the Examiner. In response, Applicants reply that they have answered such 'general' concerns by providing facts specific to PSCA and that the specific teachings of an art greatly outweigh less pertinent general concerns.

Next, the Applicants turn to the Forman/Wands analysis.

The *Forman/Wands* Analysis

(i) Level of Skill in the Art.

Applicants believe that the relative skill and experience of those in the art of peptide vaccine development is very high. Such work is typically conducted by research enterprises populated with persons with advanced doctoral and medical training in the relevant fields.

(ii) Nature of the Invention.

The invention is in the field of polypeptide vaccine development. This field of art, drug development, is traditionally one in which a large volume of screening is both typical and routine. It is a field in which the courts have held that the necessary showing for enablement does not require testing in humans[2].

(iii) Breadth of the claims.

Claim 1 is drawn to methods of inducing a cellular immune response. Without acquiescing to the position of the Examiner, and in order to expedite prosecution of the Application, the Applicants have canceled those claims which depend from claim 1 and set forth peptide fragments which do not embrace a PSCA fragment embraced by a polypeptide fragment shown to be active as discussed above in one of the above studies.

Claim 78 is drawn in part to methods of inducing an immune response. Without acquiescing on the merits and in order to expedite prosecution of the Application the Applicants have canceled those claims which depend from claim 78 and do not recite a peptide fragment

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2 Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer (In re Brana 34 U.S.P.Q. 2nd 1436 (Fed. Cir. 1995)).

See Scott v. Finney, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("Testing for the full safety and effectiveness of a prosthetic device is more properly left to the Food and Drug Administration (FDA). Title 35 does not demand that such human testing occur within the confines of Patent and Trademark Office (PTO) proceedings.").

encompassing a PSCA epitope domain set forth in the original specification in the paragraph bridging pages 92 and 93.

(iv) Amount of Guidance Presented and (v) Working examples.

A particular claim is enabled by the disclosure in an application if the disclosure, at the time of filing, contains sufficient information so as to enable one of skill in the art to make and use the claimed invention without undue experimentation. *See, e.g., In re Wands*, 8 USPQ 2d, 1400 (Fed. Cir. 1988), or MPEP §2164.01. This disclosure need not include any working examples (*see, e.g.*, MPEP §2164.02), nor need it teach what is well known to those of skill in the art. *See, e.g.*, MPEP §2164.01.

As set forth in previous papers, the specification provides all the guidance required to practice the invention. Without revisiting earlier remarks, the specification discloses the PSCA protein sequence, methods of identifying CTL and antibody epitope motifs therein, and the importance of the elevation and specificity of PSCA expression in the subject cancers.

With respect to inducing an immune response as in claim 78, the specification also teaches all the steps necessary to induce an immune response against a PSCA protein or fragment thereof. However, the fact that the methods were not actually practiced in subjects with cancer is no bar to enablement (see, *Brana* decision). The use of a GST-PSCA polyeptide conjugate to induce a humoral response in mice without cancer is disclosed in Example 5 at page 89 of the original specification. The epitope domains of PSCA with respect to the various monoclonal antibodies is also disclosed in the paragraph bridging pages 92 and 93.

(vi) State of the Art

As discussed above, the state of the art is high enough for others in the field to have already begun to practice the claimed invention largely as taught by the specification (see, above discussion of the Thomas-Kaskel et al., Matsueda et al., and Kiessling et al. art). Additionally, with respect to antibodies against PSCA antigen in animals with PSCA expressing cancers, Zhang et al. have confirmed that vaccination with a DNA vaccine based on human PSCA and HSP70 adjuvant enhanced the antigen-specific CD8(+) T-cell response and inhibited

PSCA(+) Tumor growth in mice. (see, Zhang et al., *J Gene Med.* 9(8):715-26 (2007), enclosed with IDS).

(vii) Unpredictability of the Art.

Applicants acknowledge that no art is without its uncertainty. However, the results achieved by Thomas-Kaskel et al., Matsueda et al., Kiessling et al., and Zhang et al. show that the uncertainties posed by the Examiner were no bar to others' practice of the Applicants' methods. In particular, as discussed above, the existence of clinical studies in and of itself is strong evidence that persons in the field consider the uncertainty in the art to be acceptably low.

(viii) Undue Experimentation.

The quantity of experimentation necessary[3] to practice the invention with exemplified and non-exemplified aspects appears to be well within what is routinely performed by a person of ordinary skill in the art of therapeutics development.

(ix) Summary and Overall *Forman/Wands* Analysis.

As set forth in the MPEP §2164.01(a), the final step in making the determination that "undue experimentation" would have been needed to make and use the claimed invention is reached by weighing all the above noted factual considerations. *In re Wands,* 858 F.2d at 737, 8 USPQ2d at 737."

Considering all the above, the simple fact is that *persons in the art are using the claimed invention successfully with no sign of undue experimentation.*

[3] That some experimentation may be necessary to identify operative species does not constitute a lack of enablement. As the Federal Circuit has stated, "the key word is 'undue', not 'experimentation' " in determining whether pending claims are enabled. *Wands*, 8 U.S.P.Q.2d at 1405 (Fed. Cir. 1988). Indeed, a considerable amount of experimentation is permissible if it is merely routine, or if the specification in question provides a reasonable amount of guidance for practicing the invention.

Accordingly, Applicants respectfully request that the above rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Action believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,

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